```
erminal set to DLINK
? s bongkrekic
      S6      668  BONGKREKIC
? s heart or cardio? or cardiac
>>>File 155 processing for CARDIO? stopped at CARDIOTROFICA
         1429752  HEART
         1278806  CARDIO?
          751650  CARDIAC
      S7 2472838  HEART OR CARDIO? OR CARDIAC
? s s6 and s7
             668  S6
         2472838  S7
      S8      134  S6 AND S7
? s s8 and py<=1999
Processing
             134  S8
        37631515  PY<=1999
      S9       75  S8 AND PY<=1999
? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...examined 50 records  (50)
...completed examining records
     S10       58  RD (unique items)
? s inject? or administ? or expos? or contact?
Processing
         1158856  INJECT?
         2330095  ADMINIST?
         1525463  EXPOS?
         1316662  CONTACT?
     S11 5624757  INJECT? OR ADMINIST? OR EXPOS? OR CONTACT?
? s s10 and s11
              58  S10
         5624757  S11
     S12        3  S10 AND S11
? t s12/3,k,ab/1-3

 12/3,K,AB/1      (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2005 Dialog. All rts. reserv.

08995171   PMID: 2160810
  Inhibition of Ca2(+)-induced large-amplitude swelling of liver and heart
 mitochondria by cyclosporin is probably caused by the inhibitor binding to
mitochondrial-matrix peptidyl-prolyl cis-trans isomerase and preventing it
interacting with the adenine nucleotide translocase.
  Halestrap A P; Davidson A M
  Department of Biochemistry, School of Medical Sciences, University of
Bristol, U.K.
  Biochemical journal (ENGLAND)  May 15 1990 , 268 (1) p153-60, ISSN
0264-6021  Journal Code: 2984726R
  Publishing Model Print
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed
  1. Isolated rat liver and heart mitochondria incubated in 150 mM-KSCN
or sucrose medium in the presence of respiratory-chain inhibitors showed a
large increase in swelling when exposed to 250 microM-Ca2+. Swelling was
```

inhibited by **bongkrekic** acid and cyclosporin A in both media and by ADP in KSCN medium; the effect of ADP was reversed by carboxyatractyloside. These results demonstrate that this is a suitable technique with which to study the opening of the Ca2(+)-induced non-specific pore of the mitochondrial inner membrane and implicate the adenine nucleotide carrier in this process. 2. Titration of the rate of swelling with increasing concentrations of cyclosporin showed the number of cyclosporin-binding sites (+/- S.E.M.) in liver and **heart** mitochondria to be respectively 113.7 +/- 5.0 (n = 9) and 124.3 +/- 11.2 (n = 10) pmol/mg of protein, with a Ki of about 5 nM. 3. Liver and **heart** mitochondrial-matrix fractions were prepared free of membrane and cytosolic contamination and shown to contain cyclosporin-sensitive peptidyl-prolyl cis-trans isomerase (cyclophilin) activity. Titration of isomerase activity with cyclosporin gave values (+/- S.E.M.) of 110.6 +/- 10.1 (n = 5) and 165.4 +/- 15.0 (n = 3) pmol of enzyme/mg of liver and **heart** mitochondrial protein respectively, with a Ki of 2.5 nM. The similarity of these results to those from the swelling experiments suggest that the isomerase may be involved in the Ca2(+)-induced swelling. 4. The rapid light-scattering change induced in energized **heart** mitochondria **exposed** to submicromolar Ca2+ [Halestrap (1987) Biochem. J. 244, 159-164] was inhibited by ADP and **bongkrekic** acid, the former effect being reversed by carboxyatractyloside. These results suggest an interaction of Ca2+ with the adenine nucleotide carrier when the 'c' conformation. 5. A model is proposed in which mitochondrial peptidyl-prolyl cis-trans isomerase interacts with the adenine nucleotide carrier in the presence of Ca2+ to cause non-specific pore opening. The model also explains the involvement of the adenine nucleotide translocase in the PPi-mediated cyclosporin-insensitive increase in K+ permeability described in the preceding paper [Davidson & Halestrap (1990) Biochem. J. 268, 147-152]. 6. The physiological and pathological implications of the model are discussed in relation to reperfusion injury and cyclosporin toxicity.

Inhibition of Ca2(+)-induced large-amplitude swelling of liver and heart **mitochondria by cyclosporin is probably caused by the inhibitor binding to mitochondrial-matrix peptidyl-prolyl...**

May 15 **1990** ,

1. Isolated rat liver and **heart** mitochondria incubated in 150 mM-KSCN or sucrose medium in the presence of respiratory-chain inhibitors showed a large increase in swelling when **exposed** to 250 microM-Ca2+. Swelling was inhibited by **bongkrekic** acid and cyclosporin A in both media and by ADP in KSCN medium; the effect...

... of cyclosporin showed the number of cyclosporin-binding sites (+/- S.E.M.) in liver and **heart** mitochondria to be respectively 113.7 +/- 5.0 (n = 9) and 124.3 +/- 11.2...

...10) pmol/mg of protein, with a Ki of about 5 nM. 3. Liver and **heart** mitochondrial-matrix fractions were prepared free of membrane and cytosolic contamination and shown to contain...

...5) and 165.4 +/- 15.0 (n = 3) pmol of enzyme/mg of liver and **heart** mitochondrial protein respectively, with a Ki of 2.5 nM. The similarity of these results...

... involved in the Ca2(+)-induced swelling. 4. The rapid light-scattering change induced in energized **heart** mitochondria **exposed** to submicromolar Ca2+ [Halestrap (1987) Biochem. J. 244, 159-164] was inhibited by ADP and **bongkrekic** acid, the former effect being reversed by carboxyatractyloside. These results suggest an interaction of Ca2...

Descriptors: *Amino Acid Isomerases--metabolism--ME; *Calcium

--pharmacology--PD; *Cyclosporins--pharmacology--PD; *Mitochondria, **Heart** --physiology--PH; *Mitochondria, Liver--physiology--PH; *Mitochondrial ADP, ATP Translocases--metabolism--ME; *Mitochondrial Swelling--drug...
; Adenosine Diphosphate--pharmacology--PD; Amino Acid Isomerases --antagonists and inhibitors--AI; Animals; **Bongkrekic** Acid--pharmacology --PD; Cell Membrane Permeability; Cyclosporins--metabolism--ME; Kinetics; Light; Mitochondria, **Heart** --drug effects--DE; Mitochondria, Liver--drug effects--DE; Mitochondrial ADP, ATP Translocases --antagonists and inhibitors...

Chemical Name: Cyclosporins; Thiocyanates; **Bongkrekic** Acid; potassium thiocyanate; Sucrose; Adenosine Diphosphate; Calcium; Mitochondrial ADP, ATP Translocases; Nucleotidyltransferases; Amino Acid Isomerases...

12/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08581923 PMID: 2469463

Orientation of the N-terminal region of the membrane-bound ADP/ATP carrier protein explored by antipeptide antibodies and an arginine-specific endoprotease. Evidence that the accessibility of the N-terminal residues depends on the conformational state of the carrier.

Brandolin G; Boulay F; Dalbon P; Vignais P V

Departement de Recherche Fondamentale, Centre d'Etudes Nucleaires, Grenoble, France.

Biochemistry (UNITED STATES) Feb 7 **1989** , 28 (3) p1093-100, ISSN 0006-2960 Journal Code: 0370623

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Two peptides corresponding to the amino acid sequences 1-11 (N-terminal peptide) and 288-297 (C-terminal peptide) of beef **heart** ADP/ATP carrier have been synthesized. After coupling to ovalbumin, they were **injected** into rabbits to raise polyclonal antibodies. The specificities of the generated antibodies were tested by enzyme-linked immunosorbent assay (ELISA) and (or) Western blot. Anti-N-terminal antibodies and anti-C-terminal antibodies reacted specifically with the corresponding peptide. However, only anti-N-terminal antibodies reacted with the isolated ADP/ATP carrier; they also reacted with the membrane-bound carrier in freeze-thawed mitochondria and mitoplasts, indicating that the first 10 amino acid residues of the membrane-bound carrier in mitochondria face the cytosol. On the basis that the ADP/ATP carrier can adopt two conformations, one trapped by carboxyatractyloside (CATR conformation) and the other by **bongkrekic** acid (BA conformation), the reactivity of the anti-N-terminal antibodies to the ADP/ATP carrier in mitoplasts or freeze-thawed mitochondria was tested for each conformation of the carrier. Only in the CATR conformation was the N-terminal region of the membrane-bound carrier reactive to the N-terminal antibodies; the contrasting weak reactivity of the carrier in the BA conformation suggested that the transition from the CATR conformation to the BA conformation results in a restricted conformation of the peptide chain corresponding to the first 10 amino acid residues or its partial burying in the lipid bilayer. These immunological data were complemented by enzymatic data pertaining to proteolysis of the membrane-bound ADP/ATP carrier by an arginine-specific endoprotease.(ABSTRACT TRUNCATED AT 250 WORDS)

Feb 7 **1989** ,

... acid sequences 1-11 (N-terminal peptide) and 288-297 (C-terminal peptide) of beef **heart** ADP/ATP carrier have been synthesized. After coupling to ovalbumin, they were **injected** into rabbits to raise polyclonal antibodies. The specificities of the generated antibodies were tested by...

...carrier can adopt two conformations, one trapped by carboxyatractyloside (CATR conformation) and the other by **bongkrekic** acid (BA conformation), the reactivity of the anti-N-terminal antibodies to the ADP/ATP...

Descriptors: *Epitopes--analysis--AN; *Mitochondria, **Heart** --enzymology --EN; *Mitochondrial ADP, ATP Translocases--metabolism--ME; *Nucleotidyltransferases--metabolism--ME; *Serine Endopeptidases

12/3,K,AB/3 (Item 3 from file: 155)

05043397 PMID: 893437

Reversible inhibition of adenine nucleotide translocation by long chain acyl-CoA esters in bovine heart **mitochondria and inverted submitochondrial particles. Comparison with atractylate and** bongkrekic **acid.**

Chua B H; Shrago E

Journal of biological chemistry (UNITED STATES) Oct 10 **1977** , 252 (19) p6711-4, ISSN 0021-9258 Journal Code: 2985121R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Isolated beef **heart** mitochondria incubated with atractylate and oleoyl coenzyme A at concentrations below 5 micrometer produced an immediate and significant inhibition of adenine nucleotide translocation, whereas inhibition by **bongkrekic** acid, which required preincubation with the mitochondria, was less rapid and a concentration of 50 micrometer was required for maximum effect. In sonicated submitochondrial particles, which are inverted with the inner face of the membrane **exposed** , the adenine nucleotide translocase was much more sensitive to inhibition by **bongkrekic** acid but was now insensitive to atractylate. The characteristics of the inhibition of the adenine nucleotide translocase by oleoyl-CoA were similar qualitatively and quantitatively in isolated mitochondria and "inside out" submitochondrial particles. Thus, in contrast to both atractylate and **bongkrekic** acid which bind to the membrane asymmetrically, long chain acyl-CoA esters have the capacity to bind and inhibit the adenine nucleotide translocase from both sides of the inner mitochondrial membrane.

Reversible inhibition of adenine nucleotide translocation by long chain acyl-CoA esters in bovine heart **mitochondria and inverted submitochondrial particles. Comparison with atractylate and** bongkrekic **acid.**

Oct 10 **1977** ,

Isolated beef **heart** mitochondria incubated with atractylate and oleoyl coenzyme A at concentrations below 5 micrometer produced an immediate and significant inhibition of adenine nucleotide translocation, whereas inhibition by **bongkrekic** acid, which required preincubation with the mitochondria, was less rapid and a concentration of 50...

...effect. In sonicated submitochondrial particles, which are inverted with the inner face of the membrane **exposed** , the adenine nucleotide

translocase was much more sensitive to inhibition by **bongkrekic** acid but was now insensitive to atractylate. The characteristics of the inhibition of the adenine...

... in isolated mitochondria and "inside out" submitochondrial particles. Thus, in contrast to both atractylate and **bongkrekic** acid which bind to the membrane asymmetrically, long chain acyl-CoA esters have the capacity ...

Descriptors: *Anti-Bacterial Agents--pharmacology--PD; *Atractyloside --pharmacology--PD; * **Bongkrekic** Acid--pharmacology--PD; *Coenzyme A --pharmacology--PD; *Glycosides--pharmacology--PD; *Mitochondria, Muscle --metabolism--ME; *Mitochondrial...

Chemical Name: Anti-Bacterial Agents; Glycosides; Oleic Acids; **Bongkrekic** Acid; Atractyloside; Adenosine Triphosphate; Coenzyme A; Mitochondrial ADP, ATP Translocases; Nucleotidyltransferases

?

```
? s cyclophilin(w)d
            6257  CYCLOPHILIN
         4955883  D
      S1     303  CYCLOPHILIN(W)D
? s administer? or inject or expos? or contact?
          648255  ADMINISTER?
           13695  INJECT
         1525463  EXPOS?
         1316662  CONTACT?
      S2 3307101  ADMINISTER? OR INJECT OR EXPOS? OR CONTACT?
? s s1 and s2
             303  S1
         3307101  S2
      S3      80  S1 AND S2
? s s3 and py<=1999
Processing
              80  S3
        37631515  PY<=1999
      S4      25  S3 AND PY<=1999
? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S5       9  RD (unique items)
? t s5/3,k,ab/1-9
```

5/3,K,AB/1 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)
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13540080 PMID: 10510183

Cyclosporin A and its nonimmunosuppressive analogue N-Me-Val-4-cyclosporin A mitigate glucose/oxygen deprivation-induced damage to rat cultured hippocampal neurons.

Khaspekov L; Friberg H; Halestrap A; Viktorov I; Wieloch T

Laboratory for Experimental Brain Research, Wallenberg Neuroscience Center, Lund University Hospital, Sweden.

European journal of neuroscience (FRANCE) Sep **1999** , 11 (9) p3194-8 , ISSN 0953-816X Journal Code: 8918110

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

When mouse hippocampal neuronal cultures, 2-3 weeks in vitro, were transiently **exposed** to combined glucose and oxygen deprivation (100% argon, 5% CO2, in glucose-free medium) for 90 min, extensive neuronal degeneration had occurred after 24 h of reoxygenation. When these cultures were preincubated with cyclosporin A, a calcineurin inhibitor and a blocker of the mitochondrial permeability transition, neuronal death diminished by 30-50%. Similarly, the cyclosporin A analogue, N-Me-Val-4-cyclosporin A, a potent blocker of the mitochondrial permeability transition with no significant calcineurin blocking activity, decreased cell death by 70-80%. Both cyclosporin A and N-Me-Val-4-cyclosporin A markedly attenuated calcium-induced swelling of isolated mouse brain mitochondria by blocking the mitochondrial permeability transition. The potassium thiocyanate-stabilized binding of **cyclophilin D** to mouse brain mitochondrial membranes was completely prevented by cyclosporin A and N-Me-Val-4-cyclosporin A. Our results strongly suggest that the mitochondrial permeability transition is involved in oxygen/glucose

deprivation-induced cell death in vitro. **Cyclophilin D** and other components of the mitochondrial permeability transition may be important targets for neuroprotective and anti-ischaemic drugs.

Sep **1999** ,
When mouse hippocampal neuronal cultures, 2-3 weeks in vitro, were transiently **exposed** to combined glucose and oxygen deprivation (100% argon, 5% CO2, in glucose-free medium) for...

... mouse brain mitochondria by blocking the mitochondrial permeability transition. The potassium thiocyanate-stabilized binding of **cyclophilin D** to mouse brain mitochondrial membranes was completely prevented by cyclosporin A and N-Me-Val...
... the mitochondrial permeability transition is involved in oxygen/glucose deprivation-induced cell death in vitro. **Cyclophilin D** and other components of the mitochondrial permeability transition may be important targets for neuroprotective and...
...Enzyme No.: 5.2.1.- (Cyclophilins); EC 5.2.1.8 (Immunophilins); EC 5.2.1.8 (**cyclophilin D**)
Chemical Name: Immunosuppressive Agents; N-methyl-valyl-4-cyclosporin A; Glucose; Cyclosporine; Cyclophilins; Immunophilins; **cyclophilin D**

5/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13443919 PMID: 10406942
Import and processing of heart mitochondrial cyclophilin D .
Johnson N; Khan A; Virji S; Ward J M; Crompton M
Department of Biochemistry and Molecular Biology, University College London, London, UK.
European journal of biochemistry / FEBS (GERMANY) Jul **1999** , 263 (2) p353-9, ISSN 0014-2956 Journal Code: 0107600
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Cyclophilins are a family of cyclosporin-A-binding proteins which catalyse rotation about prolyl peptide bonds. A mitochondrial isoform in mammalian cells, **cyclophilin D** , is a component of the permeability transition pore that is formed by the adenine nucleotide translocase and the voltage-dependent anion channel at **contact** sites between the inner and outer membrane. This study investigated the submitochondrial location of **cyclophilin D** by following the fate of radiolabelled protein following import. Precursor [(35)S] **cyclophilin D** was expressed in vitro from a PCR-generated cDNA. The precursor was imported by rat heart mitochondria and processed in a single step to a 21-kDa protein that was identical (SDS/PAGE) to an in vitro expressed mature protein and a **cyclophilin D** purified from rat heart mitochondria. No further modification of the mature protein could be demonstrated. Fractionation of mitochondria following import established that **cyclophilin D** locates only to the matrix. It is concluded that **cyclophilin D** binding to the permeability transition pore must occur at the inner face of the mitochondrial inner membrane.

Import and processing of heart mitochondrial cyclophilin D .
Jul **1999** ,
...binding proteins which catalyse rotation about prolyl peptide bonds. A

mitochondrial isoform in mammalian cells, **cyclophilin D**, is a component of the permeability transition pore that is formed by the adenine nucleotide translocase and the voltage-dependent anion channel at **contact** sites between the inner and outer membrane. This study investigated the submitochondrial location of **cyclophilin D** by following the fate of radiolabelled protein following import. Precursor [(35)S] **cyclophilin D** was expressed in vitro from a PCR-generated cDNA. The precursor was imported by rat...

... protein that was identical (SDS/PAGE) to an in vitro expressed mature protein and a **cyclophilin D** purified from rat heart mitochondria. No further modification of the mature protein could be demonstrated. Fractionation of mitochondria following import established that **cyclophilin D** locates only to the matrix. It is concluded that **cyclophilin D** binding to the permeability transition pore must occur at the inner face of the mitochondrial...

...Enzyme No.: 5.2.1.- (Cyclophilins); EC 5.2.1.8 (Immunophilins); EC 5.2.1.8 (**cyclophilin D**)

Chemical Name: DNA, Complementary; Digitonin; Cyclophilins; Immunophilins ; **cyclophilin D**

5/3,K,AB/3 (Item 3 from file: 155)

13429255 PMID: 10393078

The mitochondrial permeability transition pore and its role in cell death.

Crompton M

Department of Biochemistry and Molecular Biology, University College London, Gower Street, London WC1E 6BT, U.K. m.crompton@biochemistry.ucl.ac.uk

Biochemical journal (ENGLAND) Jul 15 **1999** , 341 (Pt 2) p233-49, ISSN 0264-6021 Journal Code: 2984726R

Publishing Model Print

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

This article reviews the involvement of the mitochondrial permeability transition pore in necrotic and apoptotic cell death. The pore is formed from a complex of the voltage-dependent anion channel (VDAC), the adenine nucleotide translocase and **cyclophilin - D** (CyP-D) at **contact** sites between the mitochondrial outer and inner membranes. In vitro, under pseudopathological conditions of oxidative stress, relatively high Ca2+ and low ATP, the complex flickers into an open-pore state allowing free diffusion of low-Mr solutes across the inner membrane. These conditions correspond to those that unfold during tissue ischaemia and reperfusion, suggesting that pore opening may be an important factor in the pathogenesis of necrotic cell death following ischaemia/reperfusion. Evidence that the pore does open during ischaemia/reperfusion is discussed. There are also strong indications that the VDAC-adenine nucleotide translocase-CyP-D complex can recruit a number of other proteins, including Bax, and that the complex is utilized in some capacity during apoptosis. The apoptotic pathway is amplified by the release of apoptogenic proteins from the mitochondrial intermembrane space, including cytochrome c, apoptosis-inducing factor and some procaspases. Current evidence that the pore complex is involved in outer-membrane rupture and release of these proteins during programmed cell death is reviewed, along with indications

that transient pore opening may provoke 'accidental' apoptosis.

Jul 15 **1999** ,

... from a complex of the voltage-dependent anion channel (VDAC), the adenine nucleotide translocase and **cyclophilin - D** (CyP-D) at **contact** sites between the mitochondrial outer and inner membranes. In vitro, under pseudopathological conditions of oxidative...

...Enzyme No.: 5.2.1.- (Cyclophilins); EC 5.2.1.8 (Immunophilins); EC 5.2.1.8 (**cyclophilin D**)

Chemical Name: Porins; voltage-dependent, anion-selective channels; Cyclophilins; Immunophilins; **cyclophilin D**

5/3,K,AB/4 (Item 4 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

13416019 PMID: 10377253

Evidence that cyclophilin-A protects cells against oxidative stress.

Doyle V; Virji S; Crompton M

Department of Biochemistry and Molecular Biology, University College London, Gower Street, London WC1E 6BT, UK.

Biochemical journal (ENGLAND) Jul 1 **1999** , 341 (Pt 1) p127-32, ISSN 0264-6021 Journal Code: 2984726R

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Cyclophilin-A is the cytosolic isoform of a family of peptidylproline cis-trans-isomerases that bind cyclosporin A. This study investigates the role of cyclophilin-A in necrotic cell death, induced by 'chemical ischaemia' and by t-butylhydroperoxide. An 18-mer antisense phosphorothioate oligodeoxynucleotide was used to target a translated region of cyclophilin-A mRNA in rat neonatal cardiomyocytes. After a 24 h **exposure** to the oligonucleotide, the amount of cyclophilin-A in the cells was decreased by at least 93% as judged by immunological and enzymic criteria. For the enzyme assays, peptidyl proline cis-trans-isomerase activity was measured fluorimetrically in small (10 microl) volumes of cell extract. Immunoblots were developed with a polyclonal anti-cyclophilin-A antibody after sample isoelectric focusing and SDS/PAGE. Cyclophilin-A suppression had no effect on cyanide-plus-2-deoxyglucose-induced cell death. However, cyclophilin-A-suppressed cells were markedly more sensitive to t-butylhydroperoxide. Cyclosporin A conferred some resistance to the peroxide in both types of cell, but protection was greater in cyclophilin-A-suppressed cells, where cyclosporin A increased the survival time 2-fold. It is concluded that two cyclophilin isoforms are involved, in quite different ways, in peroxide-induced cell death. Cyclophilin-A has a protective role. Another isoform, possibly mitochondrial **cyclophilin - D** , has a deleterious role, such that blockade by cyclosporin A leads to protection.

Jul 1 **1999** ,

... a translated region of cyclophilin-A mRNA in rat neonatal cardiomyocytes. After a 24 h **exposure** to the oligonucleotide, the amount of cyclophilin-A in the cells was decreased by at...

... in peroxide-induced cell death. Cyclophilin-A has a protective role. Another isoform, possibly mitochondrial **cyclophilin - D** , has a deleterious role, such that blockade by cyclosporin A leads to protection.

...Enzyme No.: 1.8 (Immunophilins); EC 5.2.1.8 (Peptidylprolyl Isomerase); EC 5.2.1.8 (**cyclophilin D**)
Chemical Name: Cyanides; Oligodeoxyribonucleotides, Antisense; tert-Butylhydroperoxide; Cyclophilins; Immunophilins; Peptidylprolyl Isomerase; **cyclophilin D**

5/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13270670 PMID: 9927435
Regulation of Hsp90 ATPase activity by tetratricopeptide repeat (TPR)-domain co-chaperones.
Prodromou C; Siligardi G; O'Brien R; Woolfson D N; Regan L; Panaretou B; Ladbury J E; Piper P W; Pearl L H
Department of Biochemistry and Molecular Biology, University College London, Gower Street, London WC1E 6BT, UK.
EMBO journal (ENGLAND) Feb 1 **1999** , 18 (3) p754-62, ISSN 0261-4189 Journal Code: 8208664
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The in vivo function of the heat shock protein 90 (Hsp90) molecular chaperone is dependent on the binding and hydrolysis of ATP, and on interactions with a variety of co-chaperones containing tetratricopeptide repeat (TPR) domains. We have now analysed the interaction of the yeast TPR-domain co-chaperones Sti1 and Cpr6 with yeast Hsp90 by isothermal titration calorimetry, circular dichroism spectroscopy and analytical ultracentrifugation, and determined the effect of their binding on the inherent ATPase activity of Hsp90. Sti1 and Cpr6 both bind with sub-micromolar affinity, with Sti1 binding accompanied by a large conformational change. Two co-chaperone molecules bind per Hsp90 dimer, and Sti1 itself is found to be a dimer in free solution. The inherent ATPase activity of Hsp90 is completely inhibited by binding of Sti1, but is not affected by Cpr6, although Cpr6 can reactivate the ATPase activity by displacing Sti1 from Hsp90. Bound Sti1 makes direct **contact** with, and blocks access to the ATP-binding site in the N-terminal domain of Hsp90. These results reveal an important role for TPR-domain co-chaperones as regulators of the ATPase activity of Hsp90, showing that the ATP-dependent step in Hsp90-mediated protein folding occurs after the binding of the folding client protein, and suggesting that ATP hydrolysis triggers client-protein release.

Feb 1 **1999** ,
...Cpr6 can reactivate the ATPase activity by displacing Sti1 from Hsp90. Bound Sti1 makes direct **contact** with, and blocks access to the ATP-binding site in the N-terminal domain of...
...Enzyme No.: 1.3 (Adenosinetriphosphatase); EC 5.2.1.8 (Peptidylprolyl Isomerase); EC 5.2.1.8 (**cyclophilin D**)
...Chemical Name: Shock Proteins 90; Macromolecular Substances; Molecular Chaperones; stress-inducible protein 1, fungal; Adenosinetriphosphatase; Peptidylprolyl Isomerase; **cyclophilin D**

5/3,K,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12557333 PMID: 9874241

Cyclophilin - D **binds strongly to complexes of the voltage-dependent anion channel and the adenine nucleotide translocase to form the permeability transition pore.**

Crompton M; Virji S; Ward J M

Department of Biochemistry and Molecular Biology, University College London, UK. m.crompton@bsm.biochemistry.ucl.ac.uk

European journal of biochemistry / FEBS (GERMANY) Dec 1 **1998** , 258 (2) p729-35, ISSN 0014-2956 Journal Code: 0107600

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

A **cyclophilin - D** affinity matrix was employed to isolate components of the mitochondrial permeability transition pore. A cDNA encoding **cyclophilin - D** was cloned from a rat liver library and ligated into pGEX to allow expression of a glutathione S-transferase/ **cyclophilin - D** fusion protein in Escherichia coli XL1 cells. The **cyclophilin - D** in the fusion was functionally normal as judged by its peptidylprolyl cis-trans-isomerase activity and its inhibition by cyclosporin A. The fusion protein was bound to glutathione-agarose to form the **cyclophilin - D** affinity matrix. The matrix selectively bound 32-kDa proteins of mitochondrial membrane extracts, but no H2O-soluble proteins were bound. The 32-kDa band on SDS/PAGE resolved into a doublet and reacted with antibodies against the voltage-dependent anion channel (porin) and the adenine nucleotide translocase. These two proteins were also selectively retained by the affinity matrix in the presence of cyclosporin A. The thus-purified voltage-dependent anion channel, adenine nucleotide translocase and the fusion protein were incorporated into phosphatidylcholine liposomes containing fluorescein sulphonate. The proteoliposomes were permeabilized by Ca2+ plus phosphate, and this was blocked completely by cyclosporin A. These properties are identical to those of the permeability transition pore in mitochondria. It is concluded that the basic permeability transition pore structure comprises the voltage-dependent anion channel (outer membrane), adenine nucleotide translocase (inner membrane) and **cyclophilin - D** , and forms at **contact** sites between the two membranes.

Cyclophilin - D **binds strongly to complexes of the voltage-dependent anion channel and the adenine nucleotide translocase...**

Dec 1 **1998** ,

A **cyclophilin - D** affinity matrix was employed to isolate components of the mitochondrial permeability transition pore. A cDNA encoding **cyclophilin - D** was cloned from a rat liver library and ligated into pGEX to allow expression of a glutathione S-transferase/ **cyclophilin - D** fusion protein in Escherichia coli XL1 cells. The **cyclophilin - D** in the fusion was functionally normal as judged by its peptidylprolyl cis-trans-isomerase activity...

... inhibition by cyclosporin A. The fusion protein was bound to glutathione-agarose to form the **cyclophilin - D** affinity matrix. The matrix selectively bound 32-kDa proteins of mitochondrial membrane extracts, but no...

... structure comprises the voltage-dependent anion channel (outer membrane), adenine nucleotide translocase (inner membrane) and **cyclophilin - D** , and forms at **contact** sites between the two membranes.

...Enzyme No.: 5.2.1.- (Cyclophilins); EC 5.2.1.8 (Immunophilins); EC 5.2.1.8 (**cyclophilin D**)

...Chemical Name: Fusion Proteins; proteoliposomes; voltage-dependent, anion-selective channels; Cyclosporine; Mitochondrial ADP, ATP Translocases ; Cyclophilins; Immunophilins; **cyclophilin D**

5/3,K,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12270650 PMID: 9575230
Chemical modification of arginines by 2,3-butanedione and phenylglyoxal causes closure of the mitochondrial permeability transition pore.
Eriksson O; Fontaine E; Bernardi P
Consiglio Nazionale delle Ricerche Unit for the Study of Biomembranes and the Laboratory of Biophysics and Membrane Biology, Department of Biomedical Sciences, University of Padova Medical School, Viale Giuseppe Colombo 3, I-35121 Padova, Italy.
Journal of biological chemistry (UNITED STATES) May 15 **1998** , 273 (20) p12669-74, ISSN 0021-9258 Journal Code: 2985121R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We have investigated the role of arginine residues in the regulation of the mitochondrial permeability transition pore, a cyclosporin A-sensitive inner membrane channel. Isolated rat liver mitochondria were treated with the arginine-specific chemical reagent 2, 3-butanedione or phenylglyoxal, followed by removal of excess free reagent. After this treatment, mitochondria accumulated Ca2+ normally, but did not undergo permeability transition following depolarization, a condition that normally triggers opening of the permeability transition pore. Inhibition by 2,3-butanedione and phenylglyoxal correlated with matrix pH, suggesting that the relevant arginine(s) are **exposed** to the matrix aqueous phase. Inhibition by 2,3-butanedione was potentiated by borate and was reversed upon its removal, whereas inhibition by phenylglyoxal was irreversible. Treatment with 2,3-butanedione or phenylglyoxal after induction of the permeability transition by Ca2+ overload resulted in pore closure despite the presence of 0.5 mM Ca2+. At concentrations that were fully effective at inhibiting the permeability transition, these arginine reagents (i) had no effect on the isomerase activity of **cyclophilin D** and (ii) did not affect the rate of ATP translocation and hydrolysis, as measured by the production of a membrane potential upon ATP addition in the presence of rotenone. We conclude that reaction with 2,3-butanedione and phenylglyoxal results in a stable chemical modification of critical arginine residue(s) located on the matrix side of the inner membrane, which, in turn, strongly favors a closed state of the pore.

May 15 **1998** ,
... 3-butanedione and phenylglyoxal correlated with matrix pH, suggesting that the relevant arginine(s) are **exposed** to the matrix aqueous phase. Inhibition by 2,3-butanedione was potentiated by borate and...
... the permeability transition, these arginine reagents (i) had no effect on the isomerase activity of **cyclophilin D** and (ii) did not affect the rate of ATP translocation and hydrolysis, as measured by...

5/3,K,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12246047 PMID: 9547337

The permeability transition pore complex: a target for apoptosis regulation by caspases and bcl-2-related proteins.

Marzo I; Brenner C; Zamzami N; Susin S A; Beutner G; Brdiczka D; Remy R; Xie Z H; Reed J C; Kroemer G

Centre National de la Recherche Scientifique, Unite Propre de Recherche 420, F-94801 Villejuif, France.

Journal of experimental medicine (UNITED STATES) Apr 20 **1998** , 187 (8) p1261-71, ISSN 0022-1007 Journal Code: 2985109R

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Early in programmed cell death (apoptosis), mitochondrial membrane permeability increases. This is at least in part due to opening of the permeability transition (PT) pore, a multiprotein complex built up at the **contact** site between the inner and the outer mitochondrial membranes. The PT pore has been previously implicated in clinically relevant massive cell death induced by toxins, anoxia, reactive oxygen species, and calcium overload. Here we show that PT pore complexes reconstituted in liposomes exhibit a functional behavior comparable with that of the natural PT pore present in intact mitochondria. The PT pore complex is regulated by thiol-reactive agents, calcium, **cyclophilin D** ligands (cyclosporin A and a nonimmunosuppressive cyclosporin A derivative), ligands of the adenine nucleotide translocator, apoptosis-related endoproteases (caspases), and Bcl-2-like proteins. Although calcium, prooxidants, and several recombinant caspases (caspases 1, 2, 3, 4, and 6) enhance the permeability of PT pore-containing liposomes, recombinant Bcl-2 or Bcl-XL augment the resistance of the reconstituted PT pore complex to pore opening. Mutated Bcl-2 proteins that have lost their cytoprotective potential also lose their PT modulatory capacity. In conclusion, the PT pore complex may constitute a crossroad of apoptosis regulation by caspases and members of the Bcl-2 family.

Apr 20 **1998** ,

... to opening of the permeability transition (PT) pore, a multiprotein complex built up at the **contact** site between the inner and the outer mitochondrial membranes. The PT pore has been previously...

... present in intact mitochondria. The PT pore complex is regulated by thiol-reactive agents, calcium, **cyclophilin D** ligands (cyclosporin A and a nonimmunosuppressive cyclosporin A derivative), ligands of the adenine nucleotide translocator...

5/3,K,AB/9 (Item 9 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

11953508 PMID: 9237665

Nitric oxide induces apoptosis via triggering mitochondrial permeability transition.

Hortelano S; Dallaporta B; Zamzami N; Hirsch T; Susin S A; Marzo I; Bosca L; Kroemer G

CNRS-UPR420, Villejuif, France.

FEBS letters (NETHERLANDS) Jun 30 **1997** , 410 (2-3) p373-7, ISSN 0014-5793 Journal Code: 0155157

Publishing Model Print

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Nitric oxide (NO) induces apoptosis in thymocytes, peripheral T cells, myeloid cells and neurons. Here we show that NO is highly efficient in inducing mitochondrial permeability transition, thereby causing the liberation of apoptogenic factors from mitochondria which can induce nuclear apoptosis (DNA condensation and DNA fragmentation) in isolated nuclei in vitro. In intact thymocytes, NO triggers disruption of the mitochondrial transmembrane potential, followed by hypergeneration of reactive oxygen species, **exposure** of phosphatidyl serine on the outer plasma membrane leaflet, and nuclear apoptosis. Inhibitors of mitochondrial permeability transition such as bongkrekic acid and a **cyclophilin D** -binding cyclosporin A derivative, N-methyl-Val-4-cyclosporin A, prevent the mitochondrial as well as all post-mitochondrial signs of apoptosis induced by NO including nuclear DNA fragmentation and **exposure** of phosphatidylserine residues on the cell surface. These findings indicate that NO can cause apoptosis via triggering of permeability transition.

Jun 30 **1997** ,

... NO triggers disruption of the mitochondrial transmembrane potential, followed by hypergeneration of reactive oxygen species, **exposure** of phosphatidyl serine on the outer plasma membrane leaflet, and nuclear apoptosis. Inhibitors of mitochondrial permeability transition such as bongkrekic acid and a **cyclophilin D** -binding cyclosporin A derivative, N-methyl-Val-4-cyclosporin A, prevent the mitochondrial as well as all post-mitochondrial signs of apoptosis induced by NO including nuclear DNA fragmentation and **exposure** of phosphatidylserine residues on the cell surface. These findings indicate that NO can cause apoptosis...
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PLEASE ENTER A COMMAND OR BE LOGGED OFF IN 5 MINUTES
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TIMEOUT: Logged Off 08/29/05 13:19:48 by System

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Set      Items   Description
S1     2213572   CARDIO? OR HEART
S2        6257   CYCLOPHILIN
S3         336   S1 AND S2
S4         186   S3 AND PY<=1999
S5         143   RD (unique items)
S6     1806501   CARDIOMYOPATHY OR CARDIAC OR HEART
S7         120   S5 AND S6
S8         108   S7 AND PY<1999
S9     5459307   TREAT?
S10         40   S5 AND S9
? s cyclophilin(w)d
            6257  CYCLOPHILIN
         4955883  D
     S11     303  CYCLOPHILIN(W)D
? s s10 and s11
              40  S10
             303  S11
     S12       5  S10 AND S11
? t s12/3,k,ab/1-15
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12/3,K,AB/1 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

13389194 PMID: 10349859

Differences in the activation of the mitochondrial permeability transition among brain regions in the rat correlate with selective vulnerability.

Friberg H; Connern C; Halestrap A P; Wieloch T

Wallenberg Neuroscience Center, Lund University, and Department of Anesthesiology, Lund University Hospital, Sweden.

Journal of neurochemistry (UNITED STATES) Jun **1999** , 72 (6) p2488-97, ISSN 0022-3042 Journal Code: 2985190R

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Mitochondria from different regions of the brain were prepared, and the activation of the mitochondrial permeability transition (MPT) by calcium was investigated by monitoring the associated mitochondrial swelling. In general, the properties of the MPT in brain mitochondria were found to be qualitatively similar to those observed in liver and **heart** mitochondria. Thus, swelling was inhibited by adenine nucleotides (AdNs) and low pH (<7.0), whereas thiol reagents and alkalosis facilitated swelling. Cyclosporin A and its nonimmunosuppressive analogue N-methyl-Val-4-cyclosporin A (PKF 220-384) both inhibited swelling and prevented the translocation of **cyclophilin D** from the matrix to the membranes of cortical mitochondria. However, the calcium sensitivity of the MPT differed in mitochondria from three brain regions (hippocampus > cortex > cerebellum) and is correlated with the susceptibility of these regions to ischemic damage. Depleting mitochondria of AdNs by **treatment** with pyrophosphate ions sensitized the MPT to [Ca2+] and abolished regional differences, implying regional differences in mitochondrial AdN content. This was confirmed by measurements showing significant differences in AdN content among regions (cerebellum > cortex > hippocampus). Our data add to recent evidence that the MPT may be involved in neuronal death.

Jun **1999** ,
... in brain mitochondria were found to be qualitatively similar to those observed in liver and **heart** mitochondria. Thus, swelling was inhibited by adenine nucleotides (AdNs) and low pH (<7.0), whereas...

... Val-4-cyclosporin A (PKF 220-384) both inhibited swelling and prevented the translocation of **cyclophilin D** from the matrix to the membranes of cortical mitochondria. However, the calcium sensitivity of the...
... correlated with the susceptibility of these regions to ischemic damage. Depleting mitochondria of AdNs by **treatment** with pyrophosphate ions sensitized the MPT to [Ca2+] and abolished regional differences, implying regional differences...

12/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13028536 PMID: 10989667
The mitochondrial permeability transition: its molecular mechanism and role in reperfusion injury.
Halestrap A P
Department of Biochemistry, University of Bristol, U.K.
Biochemical Society symposium (ENGLAND) **1999** , 66 p181-203, ISSN 0067-8694 Journal Code: 7506896
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The mitochondrial permeability transition (mPT) involves the opening of a non-specific pore in the inner membrane of mitochondria, converting them from organelles whose production of ATP sustains the cell, to instruments of death. Here, I first summarize the evidence in favour of our model for the molecular mechanism of the mPT. It is proposed that the adenine nucleotide translocase (ANT) is converted into a non-specific pore through a calcium-mediated conformational change. This requires the binding of a unique **cyclophilin** (**cyclophilin - D** , CyP-D) to the ANT, except when matrix [Ca2+] is very high. Binding of CyP-D is increased in response to oxidative stress and some thiol reagents which sensitize the mPT to [Ca2+]. Matrix adenine nucleotides decrease the sensitivity of the mPT to [Ca2+] by binding to the ANT. This is antagonized by carboxyatractyloside (an inhibitor of the ANT) and by modification of specific thiol groups on the ANT by oxidative stress or thiol reagents; such **treatments** thus enhance the mPT. In contrast, decreasing intracellular pH below 7.0 greatly desensitizes the mPT to [Ca2+]. Conditions which sensitize the mPT towards [Ca2+] are found in hearts reperfused after a period of ischaemia, a process that may irreversibly damage the **heart** (reperfusion injury). We have demonstrated directly that mPT pores open during reperfusion (but not ischaemia) using a technique that involves entrapment of [3H]deoxyglucose in mitochondria that have undergone the mPT. The mPT may subsequently reverse in hearts that recover from ischaemia/reperfusion, the extent of resealing correlating with recovery of **heart** function. A variety of agents that antagonize the mPT protect the **heart** from reperfusion injury, including cyclosporin A, pyruvate and propofol. Mitochondria that undergo the mPT and then reseal may cause cytochrome c release and thus initiate apoptosis in cells subjected to stresses less severe than those causing necrosis. An example is the apoptotic cell death in the hippocampus that occurs several days after insulin-induced hypoglycaemia, and can be prevented by prior **treatment** with cyclosporin A.

1999 ,
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... hippocampus that occurs several days after insulin-induced hypoglycaemia, and can be prevented by prior **treatment** with cyclosporin A.

12/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11349776 PMID: 8665934
Involvement of cyclophilin D **in the activation of a mitochondrial pore by Ca2+ and oxidant stress.**
Tanveer A; Virji S; Andreeva L; Totty N F; Hsuan J J; Ward J M; Crompton M
Department of Biochemistry and Molecular Biology, University College London, England.
European journal of biochemistry / FEBS (GERMANY) May 15 **1996** , 238 (1) p166-72, ISSN 0014-2956 Journal Code: 0107600
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Heart and liver mitochondria contain a structure that is able to form a large non-selective pore in the inner membrane under conditions of high matrix Ca2+ and oxidant stress. The pore is blocked by cyclosporin A (CSA). In this study, rat liver mitochondria were covalently labelled with a photoactive CSA derivative in the presence and absence of the pore ligands Ca2+ and ADP. Photolabelling of a 21-kDa protein was selectively depressed by Ca2+ in a manner reversed by ADP. The protein exhibited peptidyl-prolyl cis-trans isomerase (PPIase) activity and was inhibited by CSA (Ki, 8 nM). The PPIase was associated with the outside of sonicated submitochondrial particles but dissociated in 0.5 M NaCl. When mitochondria were **treated** with increasing concentrations of digitonin, the 21-kDa PPIase fractionated with the matrix marker enzyme, malate dehydrogenase. A second PPIase of 18 kDa fractionated with the intermembrane-space marker, adenylate kinase. Photolabelling of the 18-kDa PPIase was unaffected by Ca2+ or ADP. The 21-kDa PPIase was digested with endoproteinase Asp-N and 11 of the peptides were N-terminally sequenced. The sequences were most similar to those of human **cyclophilin** - **D** , and it is concluded that this protein is probably the CSA receptor during pore blockade by CSA. The implications of these

findings are discussed.

Involvement of cyclophilin D **in the activation of a mitochondrial pore by Ca2+ and oxidant stress.**
May 15 **1996** ,
Heart and liver mitochondria contain a structure that is able to form a large non-selective...

...outside of sonicated submitochondrial particles but dissociated in 0.5 M NaCl. When mitochondria were **treated** with increasing concentrations of digitonin, the 21-kDa PPIase fractionated with the matrix marker enzyme... ... the peptides were N-terminally sequenced. The sequences were most similar to those of human **cyclophilin - D** , and it is concluded that this protein is probably the CSA receptor during pore blockade...
...Enzyme No.: 2.1.- (Cyclophilins); EC 5.2.1.8 (Peptidylprolyl Isomerase); EC 5.2.1.8 (**cyclophilin D**)
Chemical Name: Carrier Proteins; Adenosine Diphosphate; Cyclosporine; Calcium; Amino Acid Isomerases; Cyclophilins; Peptidylprolyl Isomerase; **cyclophilin D**

12/3,K,AB/4 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06723382 Genuine Article#: ZN277 Number of References: 37
Title: Chemical modification of arginines by 2,3-butanedione and phenylglyoxal causes closure of the mitochondrial permeability transition pore (ABSTRACT AVAILABLE)
Author(s): Eriksson O; Fontaine E; Bernardi P (REPRINT)
Corporate Source: DIPARTIMENTO SCI BIOMED SPERIMENTALI,VIALE GIUSEPPE COLOMBO 3/I-35121 PADUA//ITALY/ (REPRINT); UNIV GRENOBLE 1,LAB BIOENERGET FONDAMENTALE & APPL/F-38041 GRENOBLE//FRANCE/; UNIV PADUA,SCH MED, DEPT BIOMED SCI, LAB BIOPHYS & MEMBRANE BIOL/I-35121 PADUA//ITALY/; CNR,UNIT STUDY BIOMEMBRANES/I-35121 PADUA//ITALY/
Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, **1998** , V273, N20 (MAY 15), P 12669-12674
ISSN: 0021-9258 Publication date: 19980515
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814
Language: English Document Type: ARTICLE
Abstract: We have investigated the role of arginine residues in the regulation of the mitochondrial permeability transition pore, a cyclosporin A-sensitive inner membrane channel. Isolated rat liver mitochondria were **treated** with the arginine-specific chemical reagent 2,3-butanedione or phenylglyoxal, followed by removal of excess free reagent. After this **treatment** , mitochondria accumulated Ca2+ normally, but did not undergo permeability transition following depolarization, a condition that normally triggers opening of the permeability transition pore. Inhibition by 2,3-butanedione and phenylglyoxal correlated with matrix pH, suggesting that the relevant arginine(s) are exposed to the matrix aqueous phase. Inhibition by 2,3-butanedione was potentiated by berate and was reversed upon its removal, whereas inhibition by phenylglyoxal was irreversible. **Treatment** with 2,3-butanedione or phenylglyoxal after induction of the permeability transition by Ca2+ overload resulted in pore closure despite the presence of 0.5 mM Ca2+. At concentrations that were fully effective at inhibiting the permeability transition, these arginine reagents (i) had no effect on the isomerase activity of **cyclophilin D** and (ii) did not affect the rate of ATP translocation and

hydrolysis, as measured by the production of a membrane potential upon ATP addition in the presence of rotenone, We conclude that reaction with 2,3-butanedione and phenylglyoxal results in a stable chemical modification of critical arginine residue(s) located on the matrix side of the inner membrane, which, in turn, strongly favors a closed state of the pore.

, **1998**
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...the permeability transition, these arginine reagents (i) had no effect on the isomerase activity of **cyclophilin D** and (ii) did not affect the rate of ATP translocation and hydrolysis, as measured by...
...Identifiers--CYCLOSPORINE-A; **HEART** -MITOCHONDRIA; ARGINYL RESIDUES; **CYCLOPHILIN;** MODULATION; MEMBRANE; BINDING; INHIBITION; CHANNEL; ISOMERASE

12/3,K,AB/5 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04940982 Genuine Article#: UU205 Number of References: 41
Title: INVOLVEMENT OF CYCLOPHILIN - D **IN THE ACTIVATION OF A MITOCHONDRIAL PORE BY CA2+ AND OXIDANT STRESS** (Abstract Available)
Author(s): TANVEER A; VIRJI S; ANDREEVA L; TOTTY NF; HSUAN JJ; WARD JM; CROMPTON M
Corporate Source: UNIV LONDON UNIV COLL,DEPT BIOCHEM & MOLEC BIOL,GOWER ST/LONDON WC1E 6BT//ENGLAND/; UNIV LONDON UNIV COLL,DEPT BIOCHEM & MOLEC BIOL/LONDON WC1E 6BT//ENGLAND/; LUDWIG INST CANC RES/LONDON W1P 8BT//ENGLAND/
Journal: EUROPEAN JOURNAL OF BIOCHEMISTRY, **1996** , V238, N1 (MAY), P166-172
ISSN: 0014-2956
Language: ENGLISH Document Type: ARTICLE
Abstract: **Heart** and liver mitochondria contain a structure that is able to form a large non-selective pore in the inner membrane under conditions of high matrix Ca2+ and oxidant stress. The pore is blocked by cyclosporin A (CSA). Ln this study, rat liver mitochondria were covalently labelled with a photoactive CSA derivative in the presence and absence of the pore ligands Ca2+ and ADP. Photolabelling of a 21-kDa protein was selectively depressed by Ca2+ in a manner reversed by ADP. The protein exhibited peptidyl-prolyl cis-trans isomerase (PPIase) activity and was inhibited by CSA (K-i, 8 nM). The PPIase was associated with the outside of sonicated submitochondrial particles but dissociated in 0.5 M NaCl. When mitochondria were **treated** with increasing, concentrations of digitonin, the 21-kDa PPIase fractionated with the matrix marker enzyme, malate; dehydrogenase. A second PPIase of 18 kDa fractionated with the intermembrane-space marker, adenylate kinase. Photolabelling of the 18-kDa PPIase was unaffected by Ca2+ or ADP. The 21-kDa PPIase was digested with endoproteinase Asp-N and 11 of

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Title: INVOLVEMENT OF CYCLOPHILIN - D **IN THE ACTIVATION OF A MITOCHONDRIAL PORE BY CA2+ AND OXIDANT STRESS**
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Research Fronts: 94-2560 001 (RAPAMYCIN IN T-LYMPHOCYTES; INHIBITION OF CALCINEURIN; IMMUNOSUPPRESSIVE AGENTS; MACROLIDE FK506; **CYCLOPHILIN** CYCLOSPORINE-A COMPLEX)
94-6205 001 (MITOCHONDRIAL PERMEABILITY TRANSITION PORE; CA2+ TRANSPORT; CELL CALCIUM SIGNALING)
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